UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 3 1994

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Emamectin; MK-0244 EC Insecticide; 618-EUP-RU; PP #3G04239; Temporary Tolerances for MK-0244 and its Photoproducts at 0.025 ppm in/on Cole Crops (Cabbage, Broccoli, Brussels Sprouts, and Cauliflower) and Leafy Vegetables (Celery and Lettuce);

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ACTION REQUESTED: The Registrant, Merck & Co., has submitted a number of toxicology studies to support the requested 147 acre, 10 state EUP and temporary tolerances for MK-0244 (Emamectin) and its photoproducts in/on cole crops and leafy vegetables at 0.025 ppm. Additionally, the Registrant is requesting waivers of the

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21-day dermal toxicity study in rabbits with the technical (a 24-day dermal toxicity study is available with the MK-0244 EC formulation) and the eye irritation study with MK-0244 EC formulation. Merck is citing previously submitted eye irritation studies for abamectin formulated product (Avid 1.6 EC) (Guideline Reference 81-4) as an acceptable substitute for an eye irritation study with MK-0244 EC. The eye irritation study with the abamectin formulated product had a Label Signal Word of Warning.

The Registration Division requests that Toxicology Branch-I (TB-I) address the waivers and EUP request by the Registrant and identify the requirements for essential additional toxicology studies which are needed to assess the human health risks associated with this EUP and temporary tolerances. The studies reviewed are acute, subchronic, neurotoxic, developmental, reproduction, and chronic studies performed with technical MK-0244 or formulation, MK-0244 0.16 EC, and were used to determine if the EUP program and temporary tolerances on cole crops and leafy vegetables can be toxicologically supported.

CONCLUSIONS: The EUP and temporary tolerances can be toxicologically supported.

Due to the severe eye injury and trauma to the rabbits in the primary eye irritation study with MK-0244 technical, it is likely that the Label Signal Word for MK-0244 EC will be Danger. For humane reasons, the Registrant is required to use a Label Signal Word of Danger, rather than the proposed Label Signal Word of Warning, for eye injury, plus appropriate precautionary labelling, in lieu of performing a primary eye irritation study with MK-0244 EC. The 21-day dermal toxicity study with technical MK-0244 can be waived, since the 24-day dermal toxicity study with the MK-0244 EC is acceptable for this requirement.

The margins of exposure for EUP farm workers who are involved in the 147 acre EUP program range from 30,000 to 342,860 according to exposure estimates provided by OREB (memo of July 12, 1994, attached) in comparison to the NOEL of 2.4 mg/kg/day in the 24-day dermal toxicity study in rabbits with the formulation. However, according to OREB, worker exposure for full registration is likely to be 200x the exposure estimates for the 147 acre EUP and MOEs would be considerably less for full registration.

Deoxyavermectin has been presented to the Less-than-Lifetime Committee (9/20/94). The Committee recommended the following endpoints to be used for risk assessment:

> (1) The NOEL of 0.075 mg/kg/day (L-660,599) from the 15-day dietary CF-1 mouse study for acute dietary risk assessment.

(2) The NOEL of 2.4 mg/kg/day (MK-0244) from the 24-day dermal study for occupational, residential and farm worker risk assessments for acute and subchronic dermal exposures (1-7 days and 7 days to several months).

(3) A Provisional RfD of 0.00025 mg/kg/day based on NOEL of 0.25 mg/kg/day in one year dog study and an uncertainty factor of 1000. A final RfD will be determined by the RfD Committee when the data base is finalized.

The following list gives studies that are required for the EUP and the temporary tolerances. Those studies that are satisfied are indicated. Additional studies that were submitted by the Registrant which are not required for the EUP and temporary tolerances, but are required for full registration and permanent tolerances are also included in this list. Other special studies which were submitted by the Registrant but are not Guideline requirements are not included in the requirement list.

	Technical Material	Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Partially[1]
81-2	Acute Dermal Toxicity	Yes	No[6]
81-4	Primary Eye Irritation	Yes	Yes
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes[2]	Yes
81-8	Acute Mammalian Neurotoxicity	Yes[2]	Yes
82-1(a)	Subchronic Oral (rodent)	Yes	Yes
82-1(b)	Subchronic Oral (non-rodent)	Yes	Yes
82-2	21-Day Dermal	Yes	Waived[3]
82-7	Subchronic Mammalian Neurotoxicity	Yes[2]	Yes
83-1(a)	Chronic Feeding Study (rodent)	Yes[2]	Yes
83-1(b)	Chronic Feeding Study (non-rodent)	Yes[2]	Yes
83-3(a)	Teratology (first species)	Yes	Yes
83-3(b)	Teratology (second species)	Yes[2]	Yes
83-4	Multigeneration Reproduction	Yes[2]	Yes
83-6	Developmental Neurotoxicity	Yes[2]	Yes
84-2(a)	Mutagenicity - Gene Mutation	Yes	Yes[4]
84-2(b)	Mutagenicity - Structural Chromosomal Aberrations	Yes	Yes
84-2(c)	Mutagenicity - Other Genotoxic Effects	Yes	Yes
85-1	Metabolism	Yes[2]	Yes

Formulation: MK-0244 0.16 EC Insecticide

		Required	Satisfied
81-1	Acute Oral Toxicity	Yes	Yes
81-2	Acute Dermal Toxicity	Yes	Yes
81-3	Acute Inhalation Toxicity	Yes	Yes
81-4	Primary Eye Irritation	Yes	Waived[5]
81-5	Primary Dermal Irritation	Yes	Yes
81-6	Dermal Sensitization	Yes	Yes
82-2	21-Day Dermal	Yes[2]	Yes

Comments:

1. Only females were tested. This study was graded Core Supplementary and may be upgraded to acceptable if data are provided which indicate that females are the most sensitive sex.

2. Not required for the EUP and temporary tolerance but will be required for registration and permanent tolerances.

3. This study is waived because an acceptable 24-day dermal study on the 1.94% formulation is available.

4. Some of these studies were also conducted on metabolites, polar degradates and isomers as well.

5. This study will be waived if the Registrant changes the signal word to Danger and provides the appropriate precautionary statement for the Danger signal word.

6. No acute dermal study was submitted for the Technical material. This study will not hold up the approval of the temporary tolerance and EUP, however, it will be required for full registration.

The following studies will be required for full registration:

(a) Upgrading of rat developmental neurotoxicity study with MK-0244 from Supplementary to Minimum.

(b) Dermal penetration study with MK-0244 or MK-0244 EC.

(c) Rat and mouse carcinogenicity studies with MK-0244.

(d) Upgrading acute oral study and submission of acute dermal study with MK-0244.

In addition, in consideration of farm workers (mixer/loaders and applicators), due to the low NOEL's for this chemical and to the observation that the brain, spinal cord and sciatic nerve are target organs in several species tested by the oral route and in the rabbit by the dermal route, TB-I is concerned about possible accidental exposure to the liquid formulation. TB-I suggests that the Registrant consider substituting the liquid formulation with a water-soluble solid packet. TB-I also requests that the label Signal Word be evaluated from the contents of the packet and that the precautionary statements include "Excessive exposure may result in permanent brain or nerve damage". Appropriate first aid statements are also required.

The Data Evaluation Records (DER'S) for all of the submitted studies are attached.

REVIEW:

SECTION F: - Proposed Temporary Tolerances

Based on the data reported in this petition where:

(a) Six (6) applications at 7 day intervals of up to 0.015 pounds MK-0244 active ingredient per acre (0.09 lb active ingredient/acre in a growing season) and

(b) Crops harvested 7 days after the last application.

The Petitioner, Merck & Co., requests amending 40 CFR Part 180 pursuant to Section 408 of the Federal Food, Drug and Cosmetic Act by proposing the following temporary tolerances of MK-0244/delta 8,9-isomer and the photodegradates (L-649, L-599, L-831);

COMMODITIES	TOLERANCES
Broccoli	0.025 ppm
Brussels Sprouts	0.025 ppm
Cabbage	0.025 ppm
Cauliflower	0.025 ppm
Celery	0.025 ppm
Lettuce	0.025 ppm

EUP Program: One hundred forty seven acres are being requested for this EUP program, covering areas in Southern California, Arizona, south Texas, Florida, North Carolina, New York, New Jersey, Pennsylvania, Michigan, and Colorado. The total quantity of material proposed for use is 320 quarts of formulated product (13.23 lbs ai equivalent). The material will be applied as a foliar spray by ground equipment at a rate of 0.015 lbs ai per acre. The duration of the EUP program is from August 1, 1993 to August 1, 1994.